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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/308,435	05/19/1999	HANS CARLSSON	1103326-0560	6135

7470 7590 04/04/2002
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EXAMINER

PORTNER, VIRGINIA ALLEN

ART UNIT	PAPER NUMBER
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1645

DATE MAILED: 04/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary

Application No.

09/308,435

Applicant(s)

Carlsson et al

Examiner

Partner

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Feb 21, 2002
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-38 and 45-60 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-16, 19-38, 45-49, and 53-60 is/are rejected.
- 7) ☒ Claim(s) 17, 18, and 50-52 is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some* c) ☒ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- *See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892) 18) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 19) ☐ Notice of Informal Patent Application (PTO-152)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 20) ☐ Other: _____

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DETAILED ACTION

Claims 39-44 have been canceled.

New Claims 53-60 have been submitted.

Claims 1-38, 45-60 are pending and under consideration..

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Sequence Compliance

2. The instant Application is now in sequence compliance.

Priority

3. A certified copy of an English translation of the Swedish priority document has not been received by the Office.

Objections and Rejections Withdrawn

4. Claims 4-8, 11-37, and 45-49 objected to under 37 CFR 1.75© as being in improper form because a multiple dependent claim must not depend from another multiple dependent claim and must depend from a prior claim in the alternative, in view of the amendment of the claims. See MPEP § 608.01(n).
5. Claims 51-52 rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e.,

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results in a claim which is not a proper process claim under 35 U.S.C. 101, in view of the claims having been amended to recite a methods step. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

6. Claims 39-44 rejected under 35 U.S.C. 112, first paragraph (scope), in view of the claims having been canceled.

7. Claims 1, 2, 3, 9, 38, 39, 43 and 44 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention in light of the claim amendments submitted.

8. Claims 1 and 2 and 10 rejected under 35 U.S.C. 102(e) as being anticipated by Maitra et al (US Pat. 5,874,111), in light of the claims having been amended to recite the presence of a protein, or protein fragment (dependent claims that depend from claim 1).

9. Claims 1,2,3, 9 and 10 rejected under 35 U.S.C. 102(b) as being anticipated by Wu et al (US Pat. 5,025,004) in light of the claims having been amended to recite the presence of a protein, or protein fragment (dependent claims that depend from claim 1).

Objections and Rejections Maintained

10. Claims 50-52 objected to under 37 CFR 1.75© as being in improper form because a multiple dependent claim must not depend from another multiple dependent claim and must depend from a prior claim in the alternative. See MPEP § 608.01(n). Accordingly, claims 50-52

OK

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remain withdrawn from consideration; have not been further treated on the merits. Claim 50 is a multiple dependent claim and is dependent upon claim 49 which is a multiple dependent claim; claims 51-52 are dependent upon claim 50, and therefore, also considered to multiple dependent claims that are dependent from a multiple dependent claim.

11) Claims 1 (claims 58-60 dependent claims 49, 37 and 1), 37, 38, 45-49 (claim 50 is dependent therefrom and is directed to a vaccine), 58-60 (new claims) directed to a vaccine and a method of use, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) a method of making polymer particles that comprise a protein or lipoprotein, does not reasonably provide enablement for vaccines comprising any protein from any source or any Helicobacter protein from any species or any fragment of any Helicobacter protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

12. Claim 1 rejected under 35 U.S.C. 102(a) as being anticipated by Lee et al (1998), number 6, paragraph 14 (and in view of a certified English translation of the Swedish priority document having not been received).

7,38, 45-49 (claim 50 is dependent
on 37, 50-52 new ground
amended

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W/d
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and next

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13. Claims ^{are} 1, 26-27, 36 (fragment thereof) ~~is~~ rejected under 35 U.S.C. 102(b) as being anticipated by Goldstein et al (1997) for reasons of record in paper number 6, paragraph 15, and in light of claim amendments submitted May 2001.

14. Claims 1-3, 6-7, 9, 11-14, 38, ~~49~~ are rejected under 35 U.S.C. 102(b) as being anticipated by Fountain et al (US Pat. 4,610,868) for reasons of record in paper number 6, paragraph 16.

15. Claims 38, ~~49, 58-60~~ are rejected under 35 U.S.C. 102(b) as being anticipated by Bolin et al (WO96/38475), in light of the guidance incorporated by reference to Rabinovich et al (Bolin et al page 11, lines 8-15, which teaches microcapsules vary in composition and size but are between 5 and 10 m (see Rabinovich (Science) page 6, of 15, paragraph 4, Rabinovich et al reference provided herewith, micrometers), for reasons of record in paper number 6, paragraph 19.

16. Claims 38, ~~49, 58-60~~ are rejected under 35 U.S.C. 102(b) as being anticipated by Michael et al (US Pat. 5,629,001) for reasons of record in paper number 6, paragraph 20.

Response to Arguments

17. Claims 1 (claims 58-60 dependent claims 49, 37 and 1), 37, 38, 45-49 (claim 50 is dependent therefrom and is directed to a vaccine), 58-60 (new claims) rejected under 35 U.S.C. 112, first paragraph (scope) ^{are} ~~is~~ argued by stating at page 14, last line, paragraph 5, through

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to page 15, ~~and asserts~~ that there is "sufficient disclosure to teach one of skill in the art to practice the invention", and further urges "pages 45-46, clearly demonstrate the efficacy of the claimed vaccine, i.e, the detection of antibodies against HpaA in the mucosal lining of the experimental rats."

18. It is the position of the examiner that data present on pages 45-46 is not commensurate in scope with the claimed invention that does not include cholera toxin and immunostimulation of an immune response does not define a composition as a vaccine, as patients with active infection evidence immune response to Helicobacter pylori antigens and still are infected. It was also noted that the claimed methods of administering H.pylori antigen only recite a single step, while the method exemplified in the instant specification administered the composition three times. The claimed methods do not set forth methods steps commensurate in scope with data presented in the instant specification. The claims are rejected for reasons of record as applied to claims 38-44, in light of the new claim amended submitted by Applicant.

19. The rejection of claim 1 ^{under} ~~rejected~~ 35 U.S.C. 102(a) as being anticipated by Lee et al (1998), is asserted to have been obviated through submission of an English translation of the Swedish priority document. w/d

20. It is the position of the examiner that this rejection could be obviated by submission of a ^{translation + copy} certified ~~copy~~ of the Swedish priority document, but such a document has not been submitted and made of record. This rejection is maintained for reasons of record.

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21. The rejection of claims 1, 26-27, 36 (fragment thereof) under 35 U.S.C. 102(b) as being anticipated by Goldstein et al (1997) is asserted:

to be a single step method,

to use ~~of~~ only individual amino acids of glycine or proline, and does not utilize protein or peptide antigen.

22. It is the position of the examiner that the claimed invention does not limit the claimed method to be carried sequentially, and may be carried out while mixing, wherein the mixing step and the forming droplets step could be taking simultaneously upon mixing. The "removing" step that is also recited in section (b), is carried out by Goldstein, through vacuo drying (see section 2.4.1, col. 2, page 26), a type of evaporation removing step. The method of Goldstein is not a single step method.

With respect to Applicant asserting the a protein or peptide antigen not being used in the method, it is the position of the examiner that while the base claim recites the term "protein", the dependent claims of claims 26-27 are not so limited to proteins or peptide antigens, but are directed to protein fragments. A protein fragment would encompass a single amino acid, wherein an amino acid is a fragment of a protein. The patent to Murray (1986, see col. 7, lines 41-42) teaches that antibodies to a terminal proline are known, therefore proline can be considered a type of antigen fragment of a protein, which immunoreacts with specific antibodies. The rejection is maintained for reasons of record.

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23. The rejection of claims 1-3, 6-7, 9, 11-14, ~~38, 49~~ under 35 U.S.C. 102(b) as being anticipated by Fountain et al (US Pat. 4,610,868) is asserted to not teach the methods step of "the particles are formed by dispersion of the emulsion and with the removal of the solvent."

24. It is the position of the examiner that Fountain et al teach the formation of an emulsion (see claim 96) through the combination of an aqueous phase and an organic phase (see claim 50), the resultant "globular structures" are droplet like structures. Droplets are circular in shape, thus can be considered to have a globe shape, thus the recitation of the phrase "globular structures" in the Fountain et al patent does not teach away from the claimed invention which recites the term "droplets". The droplets of Fountain et al are polymer particles that have incorporated water insoluble protein antigen, specifically lipoproteins (see claim 83). Claim limitation recited in newly amended claims 11-14 directed to the use of more than one solubilizing agent, wherein the agent is a surfactant, specifically a polyoxyethylene sorbitol compound which is taught by Fountain at col. 6, lines 40, 44 and claims 50 together with claims 67-68. The additional stabilizing agent claimed is sorbitan mono-oleate, an example of a fatty acid ester of sorbitan (see col. 6, lines 34-56 and claim 68). The size of the delivery system is taught to be from 500 nm to 100 μ m (see Fountain, col. 7, lines 25-26) which includes the recited range of 50 nm to 20 μ m. Claim 7 "alkylsulfate salt" is taught by Fountain, see col. 6, line 41. Claim 6 "sorbitan fatty acid ester" is taught by Fountain, see col. 6, line 44.

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25. The rejection of claims 38, ~~49~~, ~~58-60~~ under 35 U.S.C. 102(b) as being anticipated by Bolin et al (WO96/38475) is asserted to have been obviated through amendment of claim 38 and argues that "the vaccine delivery consists of polymer particles comprising a polymer matrix and a water insoluble protein".

26. It is the position of the examiner that Applicant's arguments are not commensurate in scope with the claimed invention that does not recite the word "consists" which recites open language "comprising". Bolin et al does disclose polymer particles as a vaccine delivery system that comprise *Helicobacter pylori* HpaA lipoprotein (see page 11, lines 8-15). No specific structural relationship of the matrix and the water insoluble antigen is required by the claims as long as the particle comprise a polymer matrix and an insoluble antigen. Bolin et al do disclose polymer particles that comprise a polymer matrix together with an *H. pylori* insoluble antigen. The rejection is maintained for reasons of record.

27. The rejection of claims 38, ~~49~~, ~~58-60~~ rejected under 35 U.S.C. 102(b) as being anticipated by Michael et al (US Pat. 5,629,001) is asserted to have been obviated through amendment of claim 38 and states the instantly claimed invention does not recite an enteric coat on the polymer particles.

28. It is the position of the examiner that Michael et al disclose polymer particles that comprises a polymer matrix, ethyl acrylate methacrylic acid copolymer (see claim 2) or polyvinylpyrrolidone (see claim 16), and a water insoluble protein antigen of *Helicobacter pylori* antigen (see Michael

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claims 1, 3 and 6; col. 8, line 18) which meets the claim limitations of claims 38, 49, 58-60. The fact that an enteric coat is used by Michael does not preclude the fact that Michael et al teaches a plurality of polymer particles. The invention of claim 38 does not require the presence of an organic solvent or linker to produce the resultant particle. The claimed product must be a polymer particle, that comprises a water insoluble protein antigen and a polymer matrix. The relationship of the matrix and the antigen is not specifically defined to be of any configuration, therefore Michael et al anticipate the now claimed invention.

New Claim Limitations/New Grounds of Rejection

Claim Rejections - 35 U.S.C. § 112

29. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

30. Claims 1, 2-10, 19-22, 24-25, 37-38, 45-49, 53-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 has been amended to recite the phrase "wherein in step (a) one or more stabilizing agents are provided in the W/O emulsion to stabilize the W/O emulsion". While the mixture of step (a) can comprise any components Applicant's may choose to recite, a "wherein" statement only provides clarification of reagents and statements previously made. As the "stabilizing

OK

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agents" have not previously been provided, the claim should recite the phrase "the mixing further comprising" rather than "wherein", to positively set forth the presence of the stabilizing agent in the mixing step (a). OK

Claims 2, 3-10, are dependent upon claim 1 and seek to further limit the number of stabilizing agents in the W/O emulsion, no stabilizing agents are specifically recited in the mixing step of section (a). This rejection could be obviated by amending section (a) of claim 1 to recite the presence of one or more stabilizing agents. OK

Claims 19-22, 37-38, 45-48, 49, 53-57, 58, 59-60 recite the claim limitations "liquid phase (X)". This phase is not defined in claim 1 from which they depend; this phrase lacks antecedent basis in claim 1. Claims 19 and 20 should be amended to recite the phrase --further comprising the steps of--- and positively recite methods steps that set forth the additional method steps needed to structurally define the double emulsion not defined in claim 1. OK

Claim 24 has been amended to recite the phrase "wherein step (b) comprises a fluid gas technique". It is not clear whether this recited technique is an additional methods step or whether it is intended to define the removing step of (b). What additional steps are intended through the recitation of the phrase "fluid gas technique"? Clarification of what this technique is, relative to the base claim is requested. OK

Claim 25 defines a Markush group of fluid gas techniques, but the terms "precipitation, "supercritical fluid", "anti-solvents" and "aerosol solvent" lack antecedent basis in claim 1 from which it depends. It appears that additional methods steps should be positively recited --further OK

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comprising the steps of--, to incorporate the additional process steps and reagents to clearly define by the recited techniques.

Claim 58 is directed to a vaccine composition that comprises the vaccine delivery system of claim 49. What is the vaccine for? Claim 49 defines the size of the polymer particles and depends from claims 37-38 (dependent upon claim 1) and 45-48 (define the polymer), wherein claim 1 broadly recite the phrase "water insoluble protein". The protein of claim 1 is not defined or claimed as a vaccine antigen associated with disease, therefore the vaccine of claim 58 is not distinctly claimed.

31. Claims 59-60 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: providing a vaccine composition for H.pylori.

32. Claims 59-60 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: providing a vaccine composition for H.pylori and correlating the immune response stimulated with treatment. Does "treatment" mean eradication of pre-existing infection, or does it mean preventing infection?

Claims 59-60 recite the phrase "an effective amount". What is the amount effective for, in light of the protein antigen of claim 58 not being so claimed to be an H.pylori vaccine antigen, but is any water insoluble protein antigen from any source?

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Please Note: Claims 4-8, 11-37 have been amended to no longer recite improper multiple dependent claim limitations and are being treated on the merits.

Claim Rejections - 35 U.S.C. § 102

33. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

34. Claims 1, 3-6, 9, 12, 19-20, 23-25, 32-38, 45-48, 49, 58 are rejected under 35

U.S.C. 102(b) as being anticipated by WO96/36317 (reference made of record in Applicant's 1449).

The claimed invention is directed to a method of producing a vaccine delivery system the method comprising the steps of:

mixing an aqueous phase with a water insoluble protein and one or more solubilizing agents with an organic phase/ polymer to produce an emulsion;

forming droplets of emulsion through dispersing the emulsion in a fluid medium; and

removing the organic solvent from the emulsion droplets to obtain polymer particles having water insoluble protein antigen incorporated therein.

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WO96/36317 disclose a method of producing a vaccine delivery system the method comprising the steps of:

mixing an aqueous phase (see page 19, Table 1) with a water insoluble protein (see page 20, lines 25-36 and page 21, lines 1-2; specifically page 21, lines 10-11) and one or more solubilizing agents (see page 22, lines 25-30) with an organic phase/ polymer (see page 12, lines 3-30 for list of polymers; page 13, lines 4-5) to produce an emulsion;

forming droplets of emulsion through dispersing (see page 24, line 22) the emulsion in a fluid medium (see page 25, lines 13-19); and

removing the organic non-solvent (see page 17, lines 1-37 (non-solvent is defined to be the organic solvent); page 11, lines 10-11 extraction vessel, page 25, line 33 from the emulsion droplets (see page 25, line 10) to obtain polymer particles (see page 25, lines 20-22) having water insoluble protein antigen incorporated therein (see page 17, lines 4-9 (non-solvent is the organic phase); page 3, lines 27-29).

The reference teaches the utilization of stabilizers together with solubility (see page 22, lines 25-31), surfactants (see page 22, lines 14-17) and bulking agents (see page 22, lines 3-31).

A three phase flow of gas, liquefied gas and frozen micro droplets defines a relationship of W/O/X (see page 15, lines 1-37 and page 16).

An additional embodiment disclosed comprise the utilization of a spray atomizer which directs the flow of liquid gas which freezes the emulsion providing means for subsequent extraction of solvent solutions to form micro particles (see page 7, lines 33-37 and top of page 8

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and page 9, lines 5-10) as well as metal cations (see page 22, lines 35-37) and a pore forming agent (see page 23, lines 6-13).

The polymers are homogenous or mixtures of polymers (see page 12, lines 3-37 and page 13, lines 1-10). The ration of the polymer to solvent (aqueous phase) is from 5% to 20% which corresponds to 1:5 or 5:100 (see page 13, lines 10-15).

The particles produced are 1 micrometer (see page 9, line 26)

The reference inherently anticipates the now claimed invention.

35. Claims 1,2-4, 11-13, 19-23, 32-38,45-48, 49, ⁵⁰53, 55, 58 are rejected under 35 U.S.C. 102(b) as being anticipated by WO95/11009 (reference made of record in Applicant's 1449). *see grounds RCB*

The claimed invention is directed to a method of producing a vaccine delivery system the method comprising the steps of:

mixing an aqueous phase with a water insoluble protein and one or more solubilizing agents with an organic phase/ polymer to produce an emulsion;

forming droplets of emulsion through dispersing the emulsion in a fluid medium; and

removing the organic solvent from the emulsion droplets to obtain polymer particles having water insoluble protein antigen incorporated therein.

WO95/11009 disclose a method of producing a vaccine delivery system the method comprising the steps of:

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mixing an aqueous phase (see figures) with a water insoluble protein (see page 3, lines 19-23) and one or more solubilizing agents (see page 5, lines 19-24) with an organic phase/ polymer (see page 4, lines 3-6 for organic phase; page 3, lines 14-18 for list of polymers;) to produce an emulsion;

forming droplets of emulsion through dispersing (see page 5, first paragraph; figures, and page 4 where first and second emulsions are formed in an emulsion bath, line 24) the emulsion in a fluid medium ;

removing the organic non-solvent (see figures, drying) to obtain polymer particles (see title) having water insoluble protein antigen incorporated therein (see page 3, lines 19-23).

The reference teaches the utilization of one or more stabilizers (see page 4, lines 25-26; and page 5, lines 1-11), together with solubilizers, specifically surfactants (see page 5, lines 19-24).

A three phase flow of gas, liquefied gas and frozen micro droplets defines a relationship of W/O/X (see page 15).

The polymers are homogenous or mixtures of polymers (see page 3, lines 14-18). The ratio aqueous phase to organic phase is described at page 6 paragraph b. Over to page 7.

The particles retained were from 25 to 150 micrometers (see page 8, first paragraph)

The reference inherently anticipates the now claimed invention.

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36. Claims 1, 2-4, 11-13, 19-23, 32-38, 45-48, 49, 53, 55, 58 are rejected under 35 U.S.C. 102(b) as being anticipated by WO95/11010 (reference made of record in Applicant's 1449).

*50 new grounds
PCT*

The claimed invention is directed to a method of producing a vaccine delivery system the method comprising the steps of:

mixing an aqueous phase with a water insoluble protein and one or more solubilizing agents with an organic phase/ polymer to produce an emulsion;

forming droplets of emulsion through dispersing the emulsion in a fluid medium; and

removing the organic solvent from the emulsion droplets to obtain polymer particles having water insoluble protein antigen incorporated therein.

WO95/11010 disclose a method of producing a vaccine delivery system the method comprising the steps of:

mixing an aqueous phase (see page 9, lines 24-28) with a water insoluble protein (see page 8, lines 15-20) and one or more solubilizing agents (see 12, lines 5-11) with an organic phase/ polymer (see Figures, and page 17, lines 10-38) to produce an emulsion;

forming droplets of emulsion through dispersing (see page 17, section D) the emulsion in a fluid medium ;

removing the organic non-solvent (see figures, drying) to obtain polymer particles (see title) having water insoluble protein antigen incorporated therein (page 12, lines 29-38).

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The reference teaches the utilization of one or more stabilizers (see page 10, lines 28; page 11, lines 32-38), together with solubilizers, specifically surfactants (page 12, lines 5-11).

A three phase flow of gas, liquefied gas and frozen micro droplets defines a relationship of W/O/X (see page 15).

The polymers are homogenous or mixtures of polymers (see page 3, lines 14-18). The ratio aqueous phase to organic phase is described at page 6 paragraph b. Over to page 7.

The particles retained were from 20-100 micrometers (see page 4, middle of page)

The reference inherently anticipates the now claimed invention.

Claim Rejections - 35 USC § 103

37. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

37, 51-52 new ground for RE and
38. Claims 1, 26-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bolin (reference of record) in light of Rabinovich et al, in view of WO96/36317 (reference made of record in Applicant's 1449).

The claimed invention is directed to methods of making polymer particles, wherein the particles include a water insoluble protein, a surfactant that is cationic, a zwitterionic or a

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chaotropic agent, and includes an *Helicobacter pylori* antigen, HpA, wherein the method comprises the steps of:

mixing an aqueous phase with a water insoluble protein and one or more solubilizing agents with an organic phase/ polymer to produce an emulsion;
forming droplets of emulsion through dispersing the emulsion in a fluid medium); and
removing the organic solvent having water insoluble protein antigen incorporated therein.

Bolin teaches a polymer matrix that comprises polymer particles for the incorporation of a *Helicobacter pylori* lipoprotein designated HpA. Bolin incorporates by reference guidance for the formulation of micro particles at page 11, paragraph 2, Rabinovich et al, Science, Vol. 265, pages 1401-1404. The Rabinovich et al reference teaches that the polymer particles are a microcapsule that maintains a protein antigen in the dry state (page 7 of 15) which provide the advantage of avoiding the need for refrigeration. The process of production is not clearly outlined but is taught to include exposure to organic solvents, incorporation of the antigen into the polymer particle and drying. Bolin et al differ from the instantly claimed invention by failing to define all of the steps in the method of making a polymer matrix containing polymer particles.

See discussion of WO96/36317 above. WO96/36317 teaches a method of making a polymer matrix that comprises polymer particles in an analogous art for the purpose of delivering a protein antigen to a mammal for stimulation of an immune response, wherein the method

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comprises the steps of mixing, forming and removing to obtain the desired polymer matrix that comprises polymer particles.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make the polymer matrix containing polymer particles that contain H.pylori lipoprotein of Bolin et al in view of the guidance and teaching provided by WO96/36317 because WO96/36317 the method of WO96/36317 produces polymer matrix containing polymer particles that a protein antigen with lower losses of biologically active agent, high product yields and is able to produce the polymer matrix containing polymer particles at the commercial scale (see WO96/36317 :page 1, lines 21-24).

The person of ordinary skill in the art would have been motivated by the reasonable expectation of success of carrying out a method that results in a high yield of polymer particles that have a lower loss rate of protein antigen during the method of making process, and results in a delivery system for an Helicobacter pylori lipoprotein antigen as taught by Bolin, because both Bolin and WO96/36317 teach that the resultant polymer particles are dried, Bolin teaches that the dried composition avoids the need for refrigeration, both methods utilize organic solvents to achieve the formulation of polymer particles that contain the protein antigen and WO96/36317 provides clear and methodical steps for the attainment of the desired polymer matrix delivery system in high product yields through the utilization of the combination of aqueous and organic solvent solutions that contain solubilizers and stabilized to attain the desired result (see discussion of WO96/36317 above).

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In the absence of a showing of unexpected results, Bolin in light of Rabinovich in view of WO96/36317 obviate the now claimed invention.

39. Claims 1, 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO96/36317 (reference made of record in Applicant's 1449) in view of Weers et al (US Pat. 6,309,623).

See discussion of WO96/36317 above. WO96/36317 teaches a method of making a polymer matrix comprising polymer particles for the delivery of a protein antigen, the method comprising the steps of mixing, forming and removing, to include the incorporation of solubilizers and stabilizers, but differs from the instantly claimed invention by failing to show the solubilizing agent to be a cationic surfactant or a chaotropic agent.

Weers et al teach the utilization of a cationic surfactant in an analogous art for the purpose of producing polymer matrix polymer particles that comprise a bioactive agent, wherein the bioactive agent can be a protein antigen.

It would have been obvious to the person ordinary skill in the art at the time the invention was made to modify the surfactant of WO96/36317 to include the cationic surfactant of Weers et al because Weers teaches that cationic surfactants may be used to enhance the association of the (alkyltrimethylammonium (col. 17, lines 20-28)) formed polymer particle with a negatively charged bioactive agent (see col. 18, lines 49-59), that charges may be used to associate the formed micro particulate with negatively charged bioactive agent, that phosphatidylcholine is a

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lipid as well as a cationic surfactant that has a gel to liquid crystal phase transition greater than about 40.degree. C, is a lipid with a relatively long chain (i.e. C₆-C₂₂) saturated lipid and provides means for the stabilization of the polymer particles(col. 16, lines 44-67).

In view of Weers et al teaching the advantages of utilizing cationic surfactants with specifically charged bioactive agents (proteins), the person of ordinary skill in the art would have been motivated by the reasonable expectation of success of obtaining a more stable polymer matrix utilizing a cationic surfactant. In the absence of a showing of unexpected results, WO96/36317 in view of Weers et al obviates the now claimed invention.

Allowable Subject Matter

40. Claims 17-18 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The prior art of record does not teach or reasonably suggest the incorporation of a chaotropic agent in to a polymer particle that comprises a water insoluble protein antigen.

Conclusion

41. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp March 27, 2002


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